IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Solomon S. Steiner and Bryan R. Wilson
Serial No.:	11/842,863
Group Art Unit:	1615
Filed:	November 21, 2003
Examiner:	SHEIKH, Humera N.
For:	*DRY POWDER FORMULATIONS OF ANTIHISTAMINE FOR NASAL ADMINISTRATION*
Confirmation No.:	**4076**
Customer No.:	**45200**

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION UNDER 37 C.F.R. § 1.132

Sir:

I, Marshall Grant, hereby declare:

1. I am a Senior Director in the Research & Development group at MannKind Corp., the assignee for the above-referenced application. I obtained a Ph.D. degree in Chemical Engineering in 1992 from Princeton University. After graduation, I worked at Exxon Corporation and returned to the Chemical Engineering Department at Princeton University as a postdoctoral fellow in 1994. From 1996 to 2001, I held the position of Assistant Professor in the Chemical Engineering Department at Yale University. Since 2001, I have been at MannKind Corporation. I have over 8 years of experience in the field of drug formulation and delivery. My Curriculum Vitae is attached (Exhibit 1).

2. As a Senior Director of the R&D Group, I have designed and helped establish some of the processes used for manufacturing of the Company's products relating to diketopiperazines as

a drug delivery system. I presently oversee and am, therefore, daily involved in the development and testing of the Company's drug/diketopiperazine delivery systems. I also have extensive knowledge of the subject matter relating to the instant application and the cited prior patent. I have read and understand the Office Action mailed on February 25, 2009 in the above-referenced application (hereinafter "the '863 application") and the references cited therein.

4. The current claims in the '863 application specifically recite a composition for the nasal administration of a drug comprising microparticles of a diketopiperazine and a drug in a dry powder form suitable for administration to the nasal mucosa, and wherein the microparticles of the dry powder have an average particle size between 10 and 20 microns and wherein more than 50% of the particles have a size greater than 10 microns for delivering to the nasal mucosa and retention of particles in the nasal cavity.

5. I understand the Examiner cited U.S. Patent No. 5,503,852 to Steiner et al. in his novelty rejection of the claims, used alone, and in view of U.S. Patent No. 5,690,954 to Illum as evidence of obviousness of the claims. The Examiner cited the Abstract; Column 4, lines 30-55; Column 10, lines 25-49 and Column 13, lines 13-24, alleging that the Steiner et al. patent discloses "drug delivery systems based on the formation of diketopiperazine microparticles and microencapsulation of drugs by derivatives of diketopiperazine, wherein the microparticles are formed in the presence of the drug to be delivered and are between 0.1 to 10 microns in diameter and whereby the microparticles are used for diagnostic applications for imaging of the nasal tract." According to the Examiner, there is no significant patentable distinction observed between the disclosure of the '863 application and the prior art since the prior art teaches drug delivery systems based on the formation of diketopiperazine microparticles and

microencapsulation of drugs by derivatives of diketopiperazine, wherein the microparticles are between 0.1 to 10 microns in diameter and are used for nasal applications. The Examiner further asserts that the 10 micron particles taught in Steiner et al. overlap in size with the 10 micron particles claimed.

6. I respectfully disagree with the Examiner's position that the reference of Steiner et al. alone or that Steiner et al. in combination with Illum discloses or suggests the claimed composition.

7. In point of fact, the claims of the '863 application are directed to microparticles for nasal delivery that differ from the microparticles disclosed in Steiner et al. In fact, the microparticles disclosed and claimed in the '863 application also differ in the method of preparation. Steiner et al. disclose that the microparticles are prepared by a method of microencapsulation of the active ingredient, which is disclosed at column 9, lines 55-67 through column 10, lines 1-8 of the reference. In point of fact, the process described by Steiner et al. is a co-precipitation method in which the diketopiperazine is dissolved in a solution and is mixed with a second solution containing an active ingredient. The resultant microparticles in Steiner et al. have the active ingredient encapsulated within the microparticles during the particle formation step by co-precipitation.

8. Secondly, the Steiner et al. microparticles are formed in an aqueous solution, contrary to the process for making the claimed microparticles. In point of fact, the claimed composition comprises microparticles which are made by a different process, one employing an organic solvent including ethanol in the reaction. Therefore, the claimed microparticles are not the same as described in Steiner et al.

9. The microparticles disclosed and claimed in Applicant's disclosure are in fact pre-formed microparticles of diketopiperazine alone in which the size of the resultant particles is tightly controlled in the crystallization reaction and particle self assembly. Accordingly, the method of the '863 application is in fact a complexation method, in which "pre-formed microparticles" are prepared and then mixed with a solution of the active ingredient so that the active ingredient can adhere or complex to the surface of the microparticle rather than being encapsulated. The complex of particle and adsorbed active ingredient is then collected by removing the solvent.

10. As a matter of fact, experiments were conducted to study the physicochemical properties of microparticles made by the method disclosed in Steiner et al. and the claimed microparticles as follows:

11. Microparticles as disclosed in Steiner et al. were made with and without an active ingredient in general accordance with the co-precipitation process described in Steiner et al. at column 15, Example 3. In point of fact, microparticles for nasal delivery as disclosed in the instant application were made by a complexation process using 2,5-diketo-3,6-di(4-fumaryl-aminobutyl)piperazine, FDKP. The FDKP was dissolved in a basic solution containing 4.7%, 7% and 18.75% ethanol and microparticles were made by mixing the FDKP-basic solution containing ethanol with an acidic solution containing an equal concentration of ethanol. After the two solutions were combined, an aliquot of glacial acetic acid, 3% of total volume, was added to the reaction mixture and the reaction mixture was allowed to mix for 1.5 hours. The precipitate that formed was collected by centrifugation, washed three times with deionized water, flash-frozen in liquid nitrogen and then dried by lyophilization to isolate pre-formed FDKP microparticles as dry powders. The lyophilized powders were then resuspended in aqueous

solution containing the active ingredient, azelastine, and the suspension was stirred at room temperature. The suspension of microparticles containing adsorbed active ingredient was flash-frozen in liquid nitrogen and then dried by lyophilization. The sizes of the microparticles in the precipitate was determined by laser diffraction and the microparticles were further analyzed by scanning electron microscopy.

TABLE 1

% Ethanol in Feed Solution	Composition	Median Particle Diameter (μm)
18.75	Suspension	50.09
	Dry powder	44.88
7.00	Suspension	24.26
	Dry powder	27.16
7.00	Suspension	not determined
	Dry powder	24.55
4.70	Suspension	15.85
	Dry powder	not determined

14. As shown in Table 1, Applicants unexpectedly found that by varying the ethanol concentration of the solution the size of the FDKP microparticles can be controlled during particle formation prior to complexation with the active ingredient, by varying the concentration of ethanol in the reaction. In fact, Applicants also surprisingly found that the average particle diameter did not vary significantly after the addition of the active ingredient. In support of these findings, Applicants further attach the reference of Wilson et al. (Respiratory Drug Delivery VIII, 2002, pages 545-548, Exhibit 2) which was published after the priority date of the '863 application. In the '863 application, the microparticles were designed to have an average particle diameter ranging between 10 and 20 μm in diameter using defined conditions.

15. Figures 1 and 2 below are scanning electron micrographs ("SEMs") of the microparticles from powders studied herewith. Figure 1 compares particles without an active ingredient that were made using ethanolic solutions (4.7% ethanol) as described in the '863 application (Figures 1a, c) and particles described by Steiner et. al. (Figures 1b, d). Not only are the particles larger when formed from ethanolic solution, the individual crystals comprising the particles have a more pronounced plate-like habit than those from aqueous solution. In Figure 2, images of pre-formed microparticles complexed with the active ingredient azelastine (Figures 2a, c) are compared with FDKP microparticles with encapsulated azelastine prepared as described by Steiner et al. (Figures 2b, d) The size and morphology of the particles are essentially the same as those prepared without the active ingredient.

Figure 1

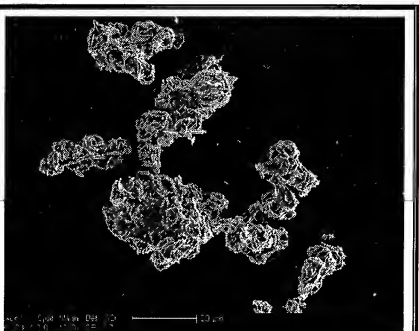


Figure 1a. FDKP particles for nasal delivery formed from ethanolic solution. (no active ingredient) (PDC FTS PR 54 1000x).

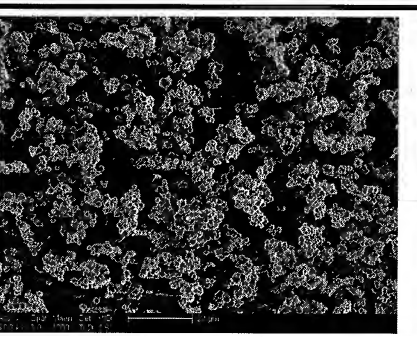


Figure 1b. FDKP particles for pulmonary delivery formed from aqueous solution (no active ingredient) (D.225.07.0004 BLANK 1000x).

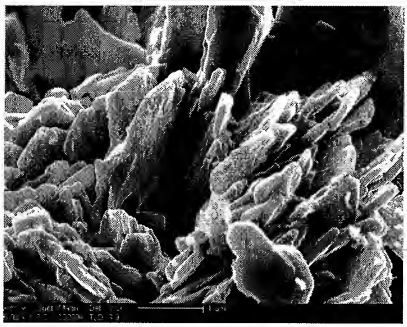


Figure 1c. FDKP particles for nasal delivery formed from ethanolic solution with no active. (MKB FTS PR 54 - 20,000x)

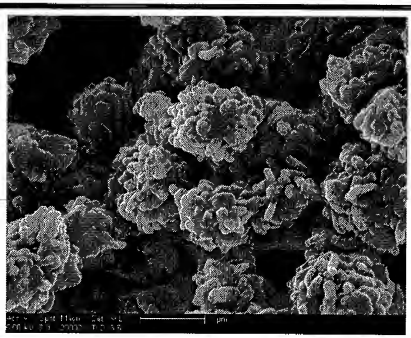


Figure 1d. FDKP particles for pulmonary delivery formed from aqueous solution (no active ingredient) D.225.07.0004 - 20,000x

Figure 2

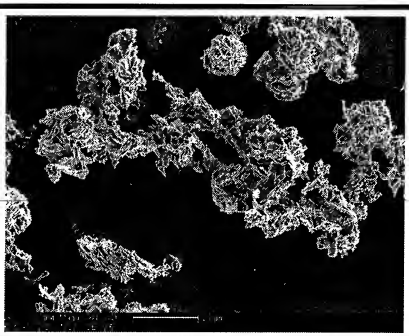


Figure 2a. FDKP particles complexed with azelastine for nasal delivery (PDC AZL Active 10 1000x).

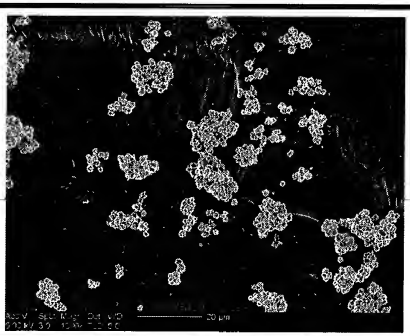


Figure 2b. FDKP particles with encapsulated azelastine prepared in the manner of Steiner et al. (ND 19783 #7 1000x).

Figure 2c. FDKP particles complexed with azelastine for nasal delivery (PDC AZL Active 10 20000x).

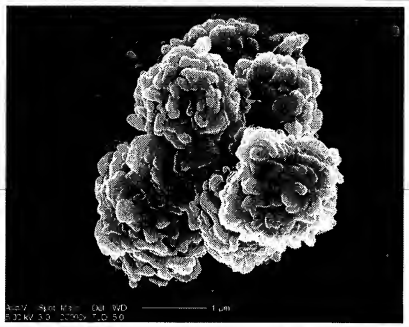


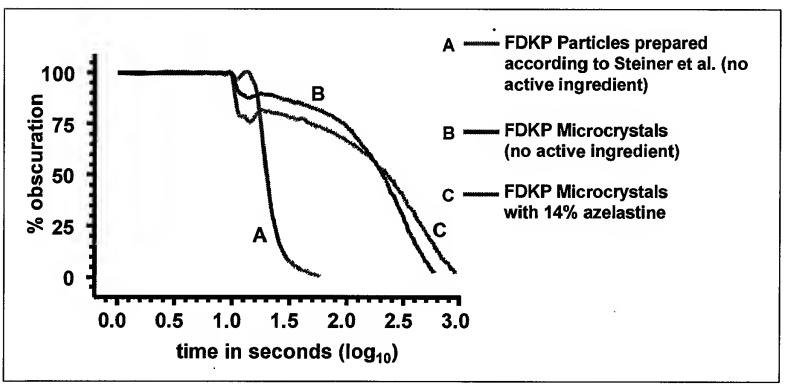
Figure 2d. FDKP particles with encapsulated azelastine prepared in the manner of Steiner et al. (ND 19783 #7 20000x .

16. As demonstrated in the SEMs, the microparticles prepared in ethanolic solutions for nasal delivery and claimed in the '863 application are in fact morphologically different in size and structure from microparticles prepared from aqueous solutions as described in Steiner et al. In fact, the SEMs show at higher magnifications that the particles for nasal delivery have a more plate-like crystal structure than the particles produced by the method disclosed in the Steiner et al. patent. Therefore, in point of fact even though the particles disclosed in Steiner overlap slightly in size at the lower end with the microparticles of the '863 application, the particles differ significantly and surprisingly in physical characteristics

17. To illustrate the differences in physical characteristics, dissolution studies were conducted in which the relative reduction in laser intensity (obscuration) of a particle suspension was monitored over time. Suspensions of each type of particle were prepared at the same particle fraction (by mass) so that 100% obscuration was attained. As the particles in the

suspension dissolved, more light was transmitted to the detector and the obscuration decreased. The results (Figure 3) indicated that FDKP particles prepared according to Steiner et al. dissolved in approximately 30 seconds ($\log_{10}$ 30 = 1.5) while the FDKP microparticles prepared from ethanolic solution as disclosed in the '863 application required approximately 500-1000 seconds (2.7-3.0 on the logarithmic axis of Figure 3). Dissolution rate is a key characteristic of solids and these differences indicate that the different processes used to prepare the FDKP microcrystals yield powders with different properties.

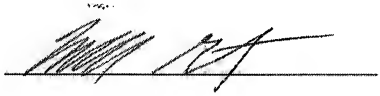
Figure 3



18. These results demonstrate that the co-precipitation-based encapsulation methods described in Steiner et al. can produce microparticles with different properties than those produced using a complexation method as disclosed in the '863 application. In fact, the disclosure of the encapsulation methods in Steiner et al. does not inherently disclose complexation or how particles for nasal delivery can be specifically made.

19. I declare that all statements made herein of my own knowledge and belief are true and that all statements made on information and belief are believed to be true, and further, that the statements are made with the knowledge that willful false statements are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: 07/23/09



Marshall Grant

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Education

Ph. D. in Chemical Engineering, Princeton University, Princeton NJ, January 1992.
M. A. in Chemical Engineering, Princeton University, Princeton NJ, January 1986.
B. S. in Chemical Engineering with highest distinction, Purdue University, West Lafayette IN, May 1984.

Experience

MannKind Corporation, Danbury CT — 7/2001 – present

Director, Formulations Research (2001-2006)
Senior Director, Formulation Development (2006-present)

- Process and product development of dry powder formulation of insulin for pulmonary delivery
  - Increased production capacity by more than 400% to meet clinical demand.
  - Improved aerodynamic performance.
  - Extended room temperature shelf life of product.
  - Contributed to CMC documents for submission to FDA and other regulatory agencies.
  - Assisted in pharmacokinetic analysis to support understanding of clinical data.
  - Participated in pre-clinical studies to evaluate formulated drug products.
- Directed feasibility studies for prospective joint ventures.
- Provided technical assessments to upper management as needed.

Yale University, New Haven CT — 1996 – 2001

Assistant Professor, Department of Chemical Engineering

- Crystallization of proteins
- Thermodynamics of protein interactions in solution and protein-surface interactions
- Colloidal phenomena

Boehringer Ingelheim Pharmaceuticals, Ridgefield CT — 1/2000 – 5/2000

Visiting Fellow, Chemical Development Department

- Solvent screening for pharmaceutical crystallization
- Drug solubility

Villanova University, Villanova, PA — 8/1995 - 12/1995

Assistant Professor (visiting), Department of Chemical Engineering

Princeton University, Princeton, NJ 1994 - 1995
Post-Doctoral Research Associate, Department of Chemical Engineering

- Experimental study of particle migration in flowing viscoelastic fluids
- Experimental study of polymer-induced flocculation of particles

Exxon Production Research Company, Houston, TX 1991 - 1994
Research Engineer (11/91 - 12/92); Senior Research Engineer (12/92 - 1/94)

- Developed and analyzed probabilistic models of oil and gas reservoirs to estimate uncertainty in oil-in-place and recovery efficiency

Publications

M.L. Grant, "Nonuniform charge effects in protein-protein interactions." *Journal of Physical Chemistry B* **105** (2001) 2858-2863.

M.L. Grant, "Effects of thermodynamic nonideality in protein crystal growth." *Journal of Crystal Growth* **209** (2000) 130-137.

M.L. Grant and D.A. Saville, "Long-term studies on tetragonal lysozyme crystals grown in quiescent and forced convection environments." *Journal of Crystal Growth* **153** (1995) 42-54.

M.L. Grant and D.A. Saville, "Electrostatic interactions between a nonuniformly charged sphere and a charged surface." *Journal of Colloid and Interface Science* **171** (1995) 35-45.

M.L. Grant and D.A. Saville, "Colloidal interactions in protein crystal growth." *Journal of Physical Chemistry* **98** (1994) 10358-10367.

M.L. Grant and D.A. Saville, "The role of transport phenomena in protein crystal growth." *Journal of Crystal Growth* **108** (1991) 8-18.

S.M. Rekhson, M.L. Grant and H.F. Peckman, "Three modes of glass failure in the glass transition region." *Glastechnische Berichte,* **56K** (1983).

Presentations, Posters and Published Abstracts

M. Grant, E. Harris, A. Leone-Bay, and K. Rousseau, "Technosphere®/Insulin: Method of Action." Diabetes Technology, Atlanta GA 2006.

A.H. Boss, M.L. Grant, and W.W. Cheatham, and A.H. Boss "Both insulin sensitivity and maximal glucose elimination rate are reduced in type 2 diabetes." American Diabetes Association, San Diego CA, 2005.

M.L. Grant and W.W. Cheatham, "Mimicry of the early phase insulin response in humans with rapidly available inhaled insulin accelerates postprandial glucose elimination compared to slower bioavailable insulin." American Diabetes Association, San Diego CA, 2005.

K.A. Leiner, P. Krueger, K. Daukas, P. Menkin, I. Trantcheva, M. Jackson, T. Vaccaro, K. Rousseau, I. Carballo, O. Gelber, M. Grant, and C. Gelber, "The pharmacokinetic profile of Technosphere®/Insulin administered by inhalation in the rat." American Diabetes Association, Orlando FL, 2004.

M. Grant, P. Menkin, I. Trantcheva, K.A. Leiner, and C. Gelber, "Distribution of ^{14}C-labeled Technosphere® particles following intra-tracheal, liquid instillation in the Sprague-Dawley Rat." American Diabetes Association, Orlando FL, May 2004.

K. Rousseau, I. Carballo, P. Robustelli, M. Grant, and C. Gelber, "Drug delivery by fumaryl diketopiperazine particles: Evidence for passive transport." American Diabetes Association, Orlando FL, May 2004.

M.L. Grant, "Implications of thermodynamic nonideality in protein crystallization." American Institute of Chemical Engineers National Meeting, Dallas TX, Nov. 1999.

M.L. Grant, "Colloidal interactions with heterogeneously charged particles." American Institute of Chemical Engineers National Meeting, Miami FL, Nov. 1998.

M.L. Grant, "Thermodynamics of dilute protein solutions from colloidal interactions." American Institute of Chemical Engineers National Meeting, Los Angeles CA, Nov. 1997.

M.L. Grant, "Protein crystal growth: Molecular interactions and transport phenomena." 1997 Yale-Hewlett Packard Conversazione on Advances in Analytical Biotechnology and Related Areas, New Haven CT, May 1997.

M.L. Grant, "Modeling protein-protein interactions in solution: An application to crystallization." American Institute of Chemical Engineers National Meeting, Chicago IL, Nov. 1996.

C.V. Deutsch and M.L. Grant, "Analysis of random function models in terms of spatial entropy." Society of Industrial and Applied Mathematics (SIAM) Minisymposium on Reservoir Characterization, Houston TX, 1993.

M.L. Grant, "The hanging drop revisited: Protein concentration gradients in an unstirred drop." 3rd Joe Wheeler Workshop on Protein Crystal Growth, Rogersville AL, 1988.

M.L. Grant and D.A. Saville, "Puzzling aspects of protein crystal growth." 2nd Joe Wheeler Workshop on Protein Crystal Growth, Rogersville AL, 1987.

S.M. Rekhson and M.L. Grant, "Fracture of glass under tension due to void formation and growth." 86th Annual Meeting of American Ceramic Society, Pittsburgh PA, 1984.

S.M. Rekhson and M.L. Grant, "Fracture of liquid glass." 85th Annual Meeting of the American Ceramic Society, Chicago IL, 1983.

Professional Activities

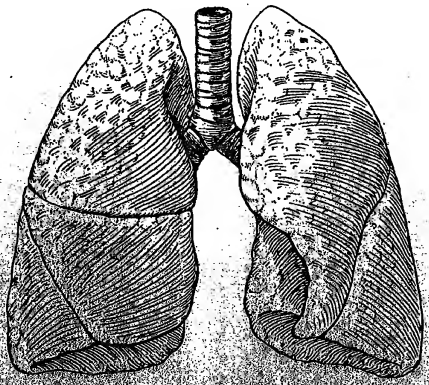
- Member, American Institute of Chemical Engineers (AIChE) and American Association of Pharmaceutical Scientists (AAPS)
- Chaired/Co-Chaired sessions on the "Crystallization of Biological and Pharmaceutical Molecules" at the AIChE Annual Meetings in 1998, 1999, and 2000.
- Chaired/Co-Chaired sessions on "Colloidal Dispersions" at the AIChE Annual Meetings in 1999 and 2000.
- Referee: *Journal of Crystal Growth, Journal of Colloid and Interface Science.*

EXHIBIT 2

Docket No. 1951300-00047

RESPIRATORY DRUG DELIVERY VIII

Biological, Pharmaceutical, Clinical, and Regulatory Issues Relating to Optimized Drug Delivery by Aerosol



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TECHNOSPHERES™ FOR PULMONARY AND NASAL APPLICATIONS

Bryan R. Wilson, Marshall L. Grant, Solomon S. Steiner, and Roderike Pohl

Pharmaceutical Discovery Corporation, Elmsford, NY and Danbury, CT, USA

INTRODUCTION

Technosphere™ is a novel and versatile drug delivery system. Technospheres have been used to stabilize and deliver peptides, proteins, and small organic molecules via pulmonary (1), oral (2), subcutaneous (3), and intravenous (4) routes of administration. They are composed of diketopiperazine derivatives that self-assemble into 2 μm spheres at low pH (5,6).

Technospheres prepared for inhalation have typical physical and aerodynamic characteristics that direct them to the deep lung. They have a mass mean aerodynamic diameter (MMAD) of 2-4 μm and a respirable fraction of delivered weight (RF%, <5.8μm) of approximately 60%, as measured by Anderson cascade impaction (7,8). Once on the lung surface, fast and efficient absorption of proteins and peptides into the systemic circulation has been demonstrated in several clinical studies (1,9).

The goal of this project was to produce larger Technosphere particles (10-100 μm diameter) for nasal inhalation (7,10,11). Decongestants and antihistamines are extremely bitter and liquid carry-over of current aerosols transports the drug to taste centers. We expect that dry powder formulations will reduce drug carry-over and more precisely target the nasal mucosa.

METHODS

Technosphere Preparation

Technosphere particles for inhalation were prepared by dissolving fumaric acid-derivatized diketopiperazine (fumaryl Technosphere or FTS) in an aqueous ammonia solution. A 10% (v/v) solution of acetic acid was prepared for precipitating the particles. The FTS and acid solutions were mixed and the formed Technospheres™ precipitated with a mean hydrodynamic diameter of approximately 2.0μm. Excess reagents and salts were removed by filtration and resuspended in fresh DI water. The slurry was then pelleted into liquid nitrogen and lyophilized to produce a light powder.

For nasal administration, the same general procedure was followed except that the FTS and acetic acid solutions were prepared in a cosolvent system of water and an organic solvent. After mixing the FTS and acetic acid solutions, an additional aliquot of glacial acetic acid was added to the mixture to induce precipitation. The washing, pelleting, and lyophilization steps were the same as above.

Scanning Electron Microscopy

Specimen mounts were prepared by spreading a drop of 0.1% poly-l-lysine over the surface of the mount. When dry, the Technosphere sample was sprinkled over the surface of the mount. The specimen was coated with 20nm carbon (Gatan 681 High Resolution Ion Beam Coater) followed by 20nm Gold/Palladium (Anatech Hummer x sputter coater). Specimens were examined using a JEOL JSM 6320F SEM with an accelerating voltage of 3.5-5.0kV.

Particle Size Distribution

The particle size distributions in aqueous suspension were determined from dynamic light scattering using a Mastersizer 2000 (Malvern Instruments Ltd., Malvern UK). A sample of the suspension was introduced via the Hydro 2000S(A) small volume sample presentation unit to attain an obscuration of approximately 20%. The data were analyzed using Malvern's general purpose model.

RESULTS

The size distributions in Figure 1 are representative of Technospheres precipitated with 10% acetic acid. Technospheres in this size range are ideal for pulmonary drug delivery and have been used for clinical trials. The addition of active pharmaceutical ingredients does not significantly change the

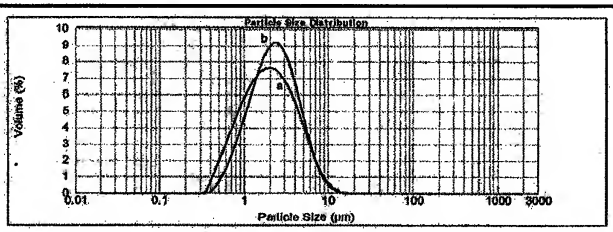

Figure 1 Overlay of hydrodynamic size distributions (Mastersizer 2000, Malvern Inst.) of Technosphere™ prepared for pulmonary delivery of insulin before (a) and after loading (b). Prior to loading, the spheres had a mean diameter of 2.5 µm, and after loading, 2.7 µm.

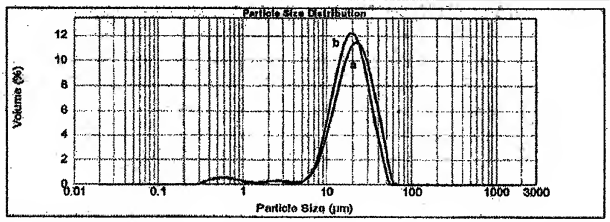

Figure 2 Overlay of hydrodynamic size distributions of Technospheres™ prepared for nasal delivery of an antihistamine before (a) and after loading (b). Prior to loading, the spheres had a mean diameter of 22.1 µm, and after loading, 19.7 µm.

size distribution of the particles in suspension. The two curves below correspond to "blank" Technosphere (a) and Technospheres with an 18% load of insulin (b).

Particle size distributions for these Technospheres again show that there is negligible difference between blank particles (curve a) and particles formulated with 14% load of a small organic molecule (curve b).

Scanning electron micrographs of Technosphere developed for inhalation and nasal application are shown in Figures 3 and 4.

Figure 3 Four Technospheres™ loaded with insulin (18% by weight) intended for pulmonary administration.

Figure 4 Group of Technospheres™ intended for nasal adminstration, unloaded.

Typical Technospheres precipitated with 10% acetic acid are shown in Figure 3; the average diameter of the primary particles is about 2 μm. In contrast, particles prepared for nasal application using a different cosolvent system have a mean hydrodynamic diameter of approximately 20 μm, with individual particles as large as 40 μm.

CONCLUSIONS

Technospheres may be formulated into small or large spheres for pulmonary, nasal, or other routes of administration by using different cosolvent systems. Loading of the spheres with pharmaceuticals does not significantly change the original size of the spheres as demonstrated by wet Malvern size distributions in Figures 1 and 2. Also, increasing the diameter of Technosphere from 2 to 20 μm, does not change the surface topography (Figure 3,4).

There are several potential advantages of Technospheres prepared for nasal inhalation over aqueous sprays. They may adhere to a specific site of action on the nasal mucosa, which can be expected to eliminate dripping of bitter tasting antihistamines into the throat. This approach should increase patient compliance and reduce the severity of side effects because a dose lower than that typically used for systemic delivery may be effective. Mixtures of different sizes may also be made to target the upper respiratory tract, as well as the deep lung. Such control over particle size makes Technosphere an extremely versatile drug delivery system.

REFERENCES

1. Steiner, S. S., Rave, K., Heise, T., Harzer, O., Flake, F., Pfuetzner, A., and Heinemann, L., (2000), "Pharmacokinetic properties and bioavailability of inhaled dry powder Technosphere™/insulin," *Exp. Clin. Endocrinol. Diabetes*, 108 (Suppl. 1), S161.

2. Rhodes, C. A., Shen, G. S., Steiner, S. S., Feldstein, R. S., and McCabe, T. R., (1994), Technosphere: Microspherical particles from substituted diketopiperazines for use in oral drug delivery," Presented at the American Chemical Society National Meeting, Washington, DC.

3. Steiner, S. S., Radwick, A. R., Jorgensen, E. J., Woods, R. W., Wilson, B. R, Jackson, M. J., and Pohl, R., (2000), "A novel glucagon delivery system for the management of hyperinsulinemia," *Diabetes*, 49 (Suppl 1), A368 #1545.

4. Lian, H, Steiner, S. S., Sofia, R. D., Woodhead, J. H., Wolf, H. H., White, H. S., Shen, G. S., Rhodes, C. A., and McCabe, R. T., "A self-complementary, self-assembling microsphere system: Application for intravenous delivery of the antiepileptic and neuroprotectant compound Felbamate," *J. Pharm. Sci.*, 89 (7), 867-875.

5. Rhodes, C. A., Steiner, S. S., Lian, H, Woods, R. J., Hijarunguru, A. V., Meroro, M. A., Lemanski, C. G., Shen, G. S., DeCosta, B. F., Saboie, D, and McCabe, R. T., (1995), "Technosphere: A self-assembling micro-particulate system for inhalation delivery of peptides and proteins in dry powder inhalers," Presented at the 26th annual meeting of the Fine Particle Society, Chicago, Ill.

6. Steiner, S. S., Rhodes, C. A., Shen, G. S., and McCabe, R. T., (1996), "Method for making self-assembling diketopiperazine drug delivery system," U.S. Patent # 5,503,852.

7. Heinemann, L., Pfuetzner, A., and Heise, T., (2001), "Alternative routes of administration as an approach to improve insulin therapy: Update on dermal, oral, nasal and pulmonary insulin delivery," *Current Pharmaceutical Design*, 7, 1327-1351.

8. Pohl, R., Muggenburg, B. A., Wilson, B. R., Woods, R. J., Burrell, B. E., and Steiner, S. S., (2000), "A dog model as a predictor of the temporal properties of pulmonary Technosphere™/insulin in humans," *Resp. Drug. Delivery VII*, Dalby, R., Byron, P., Farr, S., and Peart, J. (Eds), Serentec Press, Raleigh, NC, 463-465.

9. Rave, K. M., Heise, T., Pfuetzner, A., Steiner S. S., and Heinemann, L., (2000), "Results of a dose-response study with a new pulmonary insulin formulation and inhaler," *Diabetes*, 49 (Suppl. 1), A75.

10. Suman, J. D., Laube, B. L., Lin, T., Brouet, G., and Dalby, R., (2000), "Are *in vitro* tests of nasal solutions predictive of *in vivo* deposition?" *Resp. Drug. Delivery VII*, Dalby, R., Byron, P., Farr, S., and Peart, J. (Eds), Serentec Press, Raleigh, NC, 137-144.

11. Thorsson, L., Newman, S. P., Weisz, A., Trofast, E., and Moren, F., (1993), "Nasal distribution of Budesonide inhaled via a powder inhaler," *Rhinology*, 31, 7-10.